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# Advanced Methodologies in Pharmacovigilance

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## ABSTRACT

The World Health Organization defines pharmacovigilance as "the science and actions connected to the detection, evaluation, understanding, and prevention of adverse effects or any other drug-related problem." Pharmacovigilance is critical in ensuring that patients receive safe pharmaceuticals. We can learn more about a drug's side effects through a variety of methods, including spontaneous reporting, diligent monitoring, and database research. Novel mechanisms are being established at both the regulatory and scientific levels to increase pharmacovigilance. They include conditional approval and risk management strategies on a regulatory level, and openness and increasing patient engagement on a scientific one.

## OBJECTIVE

To review and discuss various aspects of pharmacovigilance, including new methodological developments.

***KEYWORDS:*** *spontaneous reporting, data mining in spontaneous reporting, intensive monitoring, general practice research data base, developments, international developments*

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## INTRODUCTION:

The topic of medication safety has recently received a lot of attention. Nearly frequently, stories in tabloids and scholarly publications are published about medications that induce unanticipated adverse drug responses (ADRs). These stories have had the regrettable effect of raising concerns about the usage of these medications among both patients and health professionals. A more significant outcome might be that the patient discontinues taking the recommended drug, which could lead to a condition even worse than the ADR he was initially concerned about. The World HealthOrganization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-relatedproblem," and it plays a critical role in ensuring that doctors, in collaboration with the pharmaceutical industry.

## METHODS USED IN PHARMACOVIGILANCE

Pharmacovigilance efforts are broadly classified into three categories: regulatory, industry, and academia. The goal of regulatory pharmacovigilance is to deliver medications to the public with a favourable benefit-harm profile. In this context, several regulatory post-marketing monitoring difficulties will be explored, followed by a description of the methods utilised to discover new ADRs and a review of the advantages and cons of each strategy.

There are three stages to pre-marketing clinical testing. Phase III investigations are frequently double-blind randomised controlled trials, which are regarded as the most rigorous method of assessing if a treatment-effect association exists.

However, when it comes to monitoring thesafety of a drug, this study design is not optimal. Due to the limited number of patients participating, it is generally not possible to identify ADRs that occur only rarely. The relatively short duration of clinical trials makes it difficult to detect ADRs with a long latency. Another limitationof clinical trials is the population in which a drug is tested. In order to study rare ADRs, ADRs with a long latency and ADRs in specific populations, careful monitoring ofthe drug in the post-marketing phase is essential.

Post-marketing studies can be descriptive or analytical. Descriptive studies generate hypotheses and attempt to describe the occurrence of events related to drug toxicity and efficacy. Analytical studies test hypotheses and seek to determine associations or causal connections between observed effects and particular drugs, and to measure the size of these effects. Descriptive studies are widely used in post-marketing surveillance because they are able to generate hypotheses that will become starting points for analytical studies. Two forms of descriptive studies— spontaneous reporting and intensive monitoring—will be discussed here. Analytical studies can be conducted using a variety of approaches, including case–control studies, cohort studies and clinical trials. In order to be able to conduct retrospective cohort and case–control studies, data which have been collected in a reliable and routine manner needs to be available.

## SPONTANEOUS REPORTING

In 1961, a letter from the Australian physician WG McBride was published in Lancet. In this letter, he shared his observation that babies whose mothers had used thalidomide during pregnancy were born with congenital abnormalities more often than babies who had not been exposed to thalidomide in utero [33]. In the years to come it became evident that thousands of babies had been born with limb malformations due to the maternal use of thalidomide. In order to prevent a similar disaster from occurring, systems were set up all over the world with the aim of regulating and monitoring the safety of drugs. Spontaneous reporting systems (SRS) were created, and these have become the primary method of collecting post marketing information on the safety of drugs. The main function of SRS is the early detection of signals of new, rare and serious ADRs. A spontaneous reporting system enables physicians and, increasingly more often, pharmacists and patients to report suspected ADRs to a pharmacovigilance centre. The task of the pharmacovigilance centre is to collect and analyse the reports and to inform stakeholders of the potential risk when signals of new ADRs arise.

Spontaneous reporting is also used by the pharmaceutical industry to collect information about their drugs. By using an SRS, it is feasible to monitor all medications on the market for a relatively modest cost over their full life cycle. The fundamental critique of this technique is the possibility of selective reporting and underreporting, which can lead to the incorrect conclusion that a genuine danger does not exist, while selective reporting of suspected concerns might create the impression of a risk that does not exist. Underreporting and selective reporting, on the other hand, might be viewed as benefits. When only the most severe and unexpected occurrences are reported, it is simpler to discover new ADR signals because the individual reporting the response has already identified what may be a new safety risk.

## DATA MINING IN SPONTANEOUS REPORTING

In the past, signal identification in spontaneous reporting was mostly accomplished by case-by-case analysis of reports. Yet, data mining techniques have grown in popularity in recent years. The phrase 'data mining' refers to the process of analysing data from many angles and extracting important information.

Algorithms are frequently employed in huge databases to discover hidden patterns of correlations or unexpected occurrences, i.e., signals. Although the methodology of the various data mining methods applied in pharmacovigilance differ, they all share the characteristic that they express to what extent the number of observed cases differs from the number of expected cases. Several approaches of data mining are currently in use. Proportional reporting ratios (PPRs), compare the proportion of reports for a specific ADR reported for a drug with the proportion for that ADR in all other drugs.

The calculation is analogous to that of relative risk. Using the same information, it is also possible to calculate a ‘reporting odds ratio’. The Bayesian confidence propagation neural network (BCPNN) method is used to highlight dependencies in a data set. This approach uses Bayesian statistics implemented in a neural network architecture to analyse all reported ADR combinations. Quantitatively unexpectedly strong relationships in the data are highlighted relative to general reporting of suspected adverse effects. The WHO Collaborating Centre for International Drug Monitoring uses this method for data mining. A related approach is the Multi-Item Gamma Poisson Shrinker (MGPS) used by the FDA for data mining of their spontaneous report’s database. The MGPS algorithm computes signal scores for pairs, and for higher-order (e.g., triplet, quadruplet) combinations of drugs and events that are significantly more frequent than their pair-wise associations would predict [44]. All data-mining approaches currently cannot distinguish between associations that are already known and new

associations. Moreover, clinical information described in the case reports is not taken into account; consequently, there is still the need for a reviewer to analyse these events.

## INTENSIVE MONITORING

In the late 1970s and early 1980s a new form of active surveillance was developed in New Zealand (the Intensive Medicines Monitoring Programme) and the UK (Prescription Event Monitoring). These intensive monitoring systems use prescription data to identify users of a certain drug. The prescriber of the drug is asked about any adverse event occurring during the use of the drug being monitored.These data are collected and analysed for new signals. The methodology of these intensive monitoring systems has been described in depth elsewhere [45–48]. The basis of intensive monitoring is a non-interventional observational cohort, which distinguishes it from spontaneous reportingbecause the former only monitors selected drugs during a certain period of time.

Through its non-interventional character,intensive monitoring provides real world clinical data involving neither inclusion nor exclusion criteria throughout the collection period. It is unaffected by the kind of selection and exclusion criteria that characterise clinical trials, thereby eliminating selection bias. Another strength of the methodology is that it is based upon event monitoring and is therefore capable of identifying signals for events that were not necessarily suspected as being ADRs ofthe drug being studied. Intensive monitoring programmes also enable the incidence of adverse events to be estimated, thus enabling quantification of the risk of certain ADRs. This approach, however, also has recognised limitations.The proportion of adverse effects that go unreported to doctors is unknown. The studies also produce reported event rates rather than true incident rates. This is the same for all studies based on medical record data, including computer databases and record linkage. There is no control group in standard intensive monitoring studies, and the true background incidence for events is therefore not known.

## DATA BASE STUDIES

In order to test a hypothesis, a study has to be performed. The study can be conducted using a variety of methods, including case– control studies and cohort studies. The limitations of these methods include power considerations and study design. In order to be able to conduct retrospective cohort and case–control studies, data which have been collected in a reliable and routine fashion needs to be available. The General PracticeResearch Database (GPRD) and the PHARMO Record Linkage System, which will be described in further detail in the following sections, were chosen here because they represent two different types of European databases. Other database- and record linkage systems are available for research purposes in both Europe and inNorth America.

## GENERAL PRACTICE RESEARCHDATA BASE

Virtually all patient care in the UK is coordinated by the general practitioner (GP), and data from this source provide an almost complete picture of a patient, his illnesses and treatment. Members of the GPRD, collect data from about 3 million patients (about 5% of the UK population). These patients are broadly representative of the general UK population in terms of age, sex and geographic distribution. The data collected include demographics (age and sex), medical diagnoses that are part of routine care or resulting from hospitalisations, consultations or emergency care, along with the date and location of the event. There is also an optionof adding free text, referral to hospitals and specialists, all prescriptions, including date of prescription, formulation strength, quantity and dosing instructions, indication for treatment for all new prescriptions and events leading to withdrawal of a drug or a treatment. Data on vaccinations and miscellaneous information, such as smoking, height, weight, immunisations, pregnancy, birth, death, date entering the practice, date leaving the practice and laboratory results, are also collected. A recent review of protocols using GPRD datashowed that the database is used for pharmacoepidemiology (56%), disease epidemiology (30%) and, to a lesser degree, drug utilisation, Pharmacoeconomics and environmental hazards. There have been over 250 publications in peer-reviewed journalsusing the GPRD.

## DEVELOPMENTS

Pharmacovigilance and the methods usedneed to continue to develop in order to keep up with the demands of society. In recent years, three publications have been of utmost importance in terms of providing guidance on the future of pharmacovigilance. pharmacovigilance experts from all over the world, representing different sectors, emphasise the role of communication in drug safety with the following statements:

1. Drug safety information must serve the health of the public.

2. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for health care providers.
3. All the evidence needed to assess and understand risks and benefits must be openly available.
4. Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all.
5. Innovation in drug safety monitoring needs to ensure that emerging problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated.
6. The active involvement of patients and the public in the core debate about the risks and benefits of medicines, and in decisions about their own treatment and health.
7. The development of new ways of collecting, analysing and communicating information about the safety and effectiveness of medicines; open discussion about it and the decisions which arise from it.
8. The pursuit of learning from other disciplines about how pharmacovigilance methods can be improved, alongside wide-ranging professional, official and public collaboration.
9. The creation of purposeful, coordinated, worldwide support amongst politicians, officials, scientists, clinicians, patients and the general public, based on the demonstrable benefits of pharmacovigilance to public health and patient safety.

The key values that should underpin pharmacovigilance are excellence (defined as the best possible result), the scientific method and transparency. The paper defines five elements that are considered to be essential for achieving excellence.

Three of these are: process-oriented best evidence, robust scientific decision-making and effective tools to deliver protection of public health. The other two elements, scientific development and audit, underpin these processes, recognising that excellence cannot be achieved merely by process

## INTERNATIONAL DEVELOPMENTS

In the past, pharmacovigilance has been most concerned with finding new ADRs, but pharmacovigilance should be less focused on finding harm and more focused on extending knowledge of safety. In recent years, regulatory agencies have been reforming their systems in order to keep pace with the developments in pharmacovigilance, with the focus on being more pro-active.

## EUROPE

Implementation of legal tools for monitoring the safety of medicines and for regulatory actions. Particular emphasis was placed on:

1. Systematic implementation of risk management plans
2. Strengthening the spontaneous reporting scheme through improvements of the EudraVigilance database
3. Launching the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) project to strengthen the monitoring of medicinal products
4. The conduct of multi-centre post authorisation safety studies
5. Strengthening the organisation and the operation of the EU Pharmacovigilance system in the course of the next 2 years, two main areas will be covered by the European Risk Management Strategy: further improving of the operation of the EU Pharmacovigilance System and strengthening the science that underpins the safety monitoring for medicines for human use.

## The USA

In the USA, the FDA has had a difficult time since the withdrawal of rofecoxib. The main concern is that the FDA is not able to protect the public from drug risks as efficiently as it might. In February 2007, on the basis of the IOM report, the FDA announced several initiatives designed to improve the safety of prescription drugs [26]. These initiatives fall into four main categories. The first is increasing the resources for drug safety activities.

Perceiving the agency as being overly dependent on industry funding, some observers propose eliminating user fees. The second category of proposed reform is new authority for the FDA; the agency needs regulatory tools to help assure drug safety. This authority would be exercised through a required risk 748 Eur J Clin Pharmacol (2008) 64:743–752 evaluation and mitigation strategy, including measures such as prescribing restrictions,

limits on direct consumer marketing and requirements for post-marketing studies. The FDA could impose monetary penalties for non-compliance. A third aspect of the reform is the improvement of post marketing surveillance. A routine systematic approach to active population-based drug surveillance that could identify potential safety problems is needed. Finally, changes in the FDA management practices and safety supervision are necessary.

**Involvement of patients**

Another important development is the recognition of the patient as an important player in pharmacovigilance. Patients are the users of drugs, and it is their use of a drug in a safe manner is the ultimate goal of pharmacovigilance activities. In an increasing number of countries patients are now allowed to report ADRs to the spontaneous reporting system. The European Commission acknowledges the role of the patient in spontaneous reporting.

Patients and patient organisations are becoming increasingly more involved inpharmacovigilance, especially when it comes to risk communication. After introducing patient reporting in the spontaneous reporting scheme in 2004, the Netherlands Pharmacovigilance Centre Lareb took patient reporting one step further and introduced, in 2006, an intensive monitoring programme using patients as a source of information. The Lareb intensive monitoring programme (LIM), follows the prescription-event monitoring methodology in that patients are identified on the basis of prescriptions.

Eligible patients are identified in their pharmacies when they come and pick up for the first time the drug under study. Patients can register at the LIM website, and during a certain period of time they will receive questionnaires asking them about adverse events. The system is totally web- based; consequently, questionnaires can besent via email to participating patients at different points, allowing the collection of longitudinal data. The high level of automation also allows a rapid collectionand analysis of data.

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